Impact of Policy Change on US Army Combat Transfusion Practices

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Background: Clinical practice guidelines (CPGs) are used to keep providers up-to-date with the most recent literature and to guide in decision making. Adherence is typically improved although many have a muted impact. In March 2006, the US Army issued a damage control resuscitation CPG, encouraging 1:1 plasma:red blood cell (RBC) transfusions and limiting crystalloid use. The objective of this study was to determine whether the CPG was associated with a change in the transfusion practices in combat-wounded patients.

Methods: All US service members injured in Operation Iraqi Freedom/Operation Enduring Freedom who received massive transfusions (MTs; ≥10 RBC in 24 hours) were queried from the US Army Institute of Surgical Research transfusion database. Whole blood, when used, was counted as 1 unit of RBC, fresh frozen plasma (FFP), and platelet. Subjects were divided into pre- and post-CPG cohorts. Primary outcomes were ratios of FFP:RBC and crystalloid use.

Results: A total of 777 MT patients were identified. The cohorts were similar in age (25 years ± 6 years vs. 25 years ± 6 years; p = ns) and injury severity scale score (24 ± 12 vs. 25 ± 12; p = ns). The post-CPG cohort was warmer (96.5°F ± 7.8°F vs. 98.2°F ± 1.9°F; $p < 0.05$) and was transfused more RBC, platelets, and plasma but received less crystalloid (17 units ± 12 units vs. 19 units ± 11 units, 1 unit ± 2 units vs. 2 units ± 3 units, 8 units ± 8 units vs. 14 units ± 11 units, 14 L ± 14 L vs. 9 L ± 13 L, respectively; $p < 0.05$). The post-CPG cohort also received a higher ratio transfusion (0.5 ± 0.31 vs. 0.8 ± 0.31; $p < 0.05$) representing a change in practice. Overall mortality was not different between the two groups (24 vs. 19%; $p = 0.115$).

Conclusions: MT patients are now receiving a higher FFP:RBC ratio and less crystalloid after implementation of the CPG. Additionally, patients are now presenting normothermic and have higher hemoglobin levels. All of these changes are consistent with the principles of damage control resuscitation. Changes in practice were associated with implementation of the CPG, maturity of the battlefield, and increased availability of products.

Key Words: Trauma, Trauma systems, Clinical practice guideline, Damage control resuscitation.

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Outside of large Level I trauma centers, active duty military and reservist physicians have little to no chance to practice their battlefield trauma skills when deployed. A report by the General Accounting Office found that military medical providers were not prepared to provide trauma care to severely injured soldiers in wartime.[1]

The reasons for these deficiencies are multiple but include, for one, the operational tempo of the battlefield compared with civilian trauma care. A major US Level I trauma center has between 3,500 and 5,000 evaluations per year out of a population of 2 to 5 million people for a rate of less than a quarter of a percent. However, in Iraq, a combat support hospital (CSH) evaluates ~6,500 soldiers per year out of a population of ~200,000 for a rate of >3%, i.e., >10 times as many evaluations per population.

There is also a difference in the type and severity of wounds received in combat. Combat wounds, in general, are more likely to have a penetrating mechanism necessitating operative intervention and have a greater incidence of massive transfusion (MT). A CSH typically sees 80% to 90% penetrating, 75% to 80% operative, and 3 times the MT rate compared with civilian trauma centers.[2,3]

In response to the problem, the Joint Theater Trauma System (JTTS) developed predeployment training, which includes the Emergency War Surgery course and the Joint Force Combat Trauma Management Course. The JTTS also uses clinical practice guidelines (CPGs), created from lessons learned and contemporary literature, which are incorporated into the predeployment training, distributed to those providers already deployed by digital video disc, and provided via the Web. These CPGs are periodically reviewed and updated. CPGs are summaries with recommendations but do not substitute for the clinical judgment of the clinician. They have been shown to improve outcomes in various civilian populations.[4,5]

Additionally, the JTTS holds weekly conferences to track individual patient movement through the echelons of care and monthly conferences that are system-specific. The participants in these conferences include a range of providers from the JTTS staff in the continental United States to the deployed command, military treatment facility providers, and providers throughout the evacuation chain.[6]

The aim of this study was to determine whether the performance improvement adjuncts were associated with a change in practice. There are currently 26 active CPGs on topics ranging from use of trauma flow sheets to urologic

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trauma management to initial care of ocular injuries. We selected one of the CPGs, damage control resuscitation (DCR), with metrics we could assess statistically plasma:red blood cell (RBC) ratio transfused and crystalloid use.

There has been much debate about the optimal transfusion ratio for trauma patients in the past decade, especially in MT (≥10 units RBC).[7–15] The findings of Borgman et al.[7] suggested a mortality benefit from a higher ratio plasma:RBC transfusion. From this study, a CPG was issued which encouraged physicians to adhere to the principles of DCR in patients anticipated to require an MT. The tenets of the guideline were early use of blood products during resuscitation with a goal of a plasma:RBC: ratio of 1:1, limited crystalloid use, and prevention of hypothermia.[16] Our hypothesis was that the implementation of the DCR CPG was associated with a change in resuscitation practice.

PATIENTS AND METHODS

A retrospective review of the theater transfusion database was approved by the Brooke Army Medical Center Institutional Review Board. The database includes the majority of US military patients who have received a blood transfusion in Iraq or Afghanistan since March 2003. Subjects were divided into cohorts based on the time wounded: the first cohort (pre-CPG) was treated from March 2003 to February 2006 and the second cohort (post-CPG) between March 2006 and September 2008. Data were obtained from the US Army Institute of Surgical Research (USAISR) transfusion database, the Joint Theater Trauma Registry maintained at the USAISR, and the Joint Patient Tracking Application. The Joint Theater Trauma Registry is a Department of Defense database established to prospectively collect data from multiple clinical and administrative systems. The Joint Patient Tracking Application is a Department of Defense application to record a patient's progress from the battlefield through recovery or death. A retrospective cohort analysis was performed of consecutive patients who required an MT.

Demographic, laboratory, and physiologic data as well as transfusion requirements were obtained and outcomes determined. Transfusion requirements were obtained from the USAISR transfusion database, and MT was defined as ≥10 units of packed RBCs and fresh whole blood in the initial 24 hours after admission. All patients included in the analysis were active-duty US military personnel.

Data compiled for analysis included demographic data, mechanism of injury, admission vital signs, admission laboratory tests, injury severity scale (ISS) scores, and mortality. Additionally, transfusion and fluid (crystalloid and colloid) requirements during the first 24 hours after admission were obtained. Vital signs and laboratory tests taken on admission were systolic blood pressure, pulse, respiratory rate, Glasgow coma scale, temperature (°F), hemoglobin (Hgb) concentration, base deficit, and international normalization ratio. Blood values were measured typically using i-STAT (Abbott Point-of-Care Inc., Princeton, NJ). Recorded vital signs and compiled laboratory results were the earliest available after admission to either a Level II or Level III facility as appropriate. Mechanism of injury was recorded as gunshot wound, explosion, motor vehicle collision, or other. Explosion injuries included those resulting from improvised explosive devices, mortar, mine, blast, rocket, rocket-propelled grenade, and grenade. Total transfusion requirements in the first 24 hours after admission included all blood components (units of RBC, fresh frozen plasma [FFP], and fresh whole blood). Cumulative plasma:RBC ratios were calculated with whole blood counted as 1 unit plasma, 1 unit RBC, and 1 unit platelet. Patients were also stratified into low, medium, and high transfusion ratios as previously described.[7] Total Factor VIIa use during the initial 24 hours after admission was determined. Individual ISS scores were calculated from patient medical records according to published guidelines.[17,18]

Microsoft Office Excel 2003 (Microsoft Corp, Redmond, WA) was used for database construction. Continuous variables were compared with a Student's t test or Wilcoxon test, and categorical variables were compared with χ^2 analysis using SPSS 16.0 (Cary, NC). Variables are expressed as mean ± SD, and statistical significance was set for a p value of less than 0.05.

RESULTS

Between March 2003 and September 2008, 777 consecutive MTs were performed; 351 patients (45%) in the 35 months of the pre-CPG time period and 426 MT patients (55%) in the 30 months of the post-CPG time period. This represented 30% (351 of 1,164) of patients who received a transfusion pre-CPG and 42% (426 of 1,012) of patients who received a transfusion post-CPG ($p = 0.0001$). The pre- and post-CPG groups were similar in age and ISS scores (Table 1). The pre-CPG cohort presented less tachycardic, more hypothermic, and with a lower Hgb than the post-CPG. The pre- and post-CPG groups were equally likely to be injured by an explosion compared with the other mechanisms (75% vs. 78%; $p = 0.269$; Table 2).

The post-CPG group received more units of RBCs, plasma, and platelets (Table 3 and Fig. 1). Both groups were transfused similar amounts of colloid, but the post-CPG group received less crystalloid. Factor VIIa use was the same

TABLE 1. Patient Demographics by Cohort

Variables	Pre-CPG	Post-CPG	p
Demographics	25 ± 6	25 ± 6	0.868
Age (yr)			
Injury severity score	24 ± 12	25 ± 12	0.320
Vitals			
Pulse (bpm)	110 ± 34	118 ± 72	0.012
Systolic blood pressure	107 ± 35	103 ± 37	0.194
Temperature (°F)	96.5 ± 7.8	98.2 ± 1.9	0.000
Glasgow coma scale	11 ± 5	11 ± 5	0.865
Laboratory tests			
Base deficit	−8.3 ± 7.3	−8.3 ± 7.1	0.504
International normalized ratio	1.8 ± 1.1	1.7 ± 0.9	0.308
Hemoglobin (g/dL)	10.9 ± 2.7	11.6 ± 2.9	0.001

Data are presented as mean ± SD.

TABLE 2. Mechanism by Cohort

Mechanism	Pre-CPG (%)	Post-CPG (%)
Gunshot wound	21	20
Explosion	75	78
Motor vehicle collision	4	1
Other	0	2

TABLE 3. Transfusion Data by Cohort

Transfusion Data	Pre-CPG	Post-CPG	*p*
Red blood cells (units)	17 ± 12	19 ± 11	0.011
Fresh frozen plasma (units)	8 ± 8	14 ± 11	0.000
Platelets (units)	1 ± 2	2 ± 3	0.000
Whole blood (units)	3 ± 5	3 ± 7	0.000
Cryogenic (units)	1 ± 1	1 ± 1	0.139
Crystalloid (L)	14 ± 14	9 ± 13	0.000
Colloid (mL)	481 ± 832	449 ± 738	0.270
Received whole blood	51%	30%	0.000
Received rVIIa	43%	44%	0.857
FFP:RBC	0.538 ± 0.312	0.766 ± 0.314	0.000

Data are presented as mean ± SD.

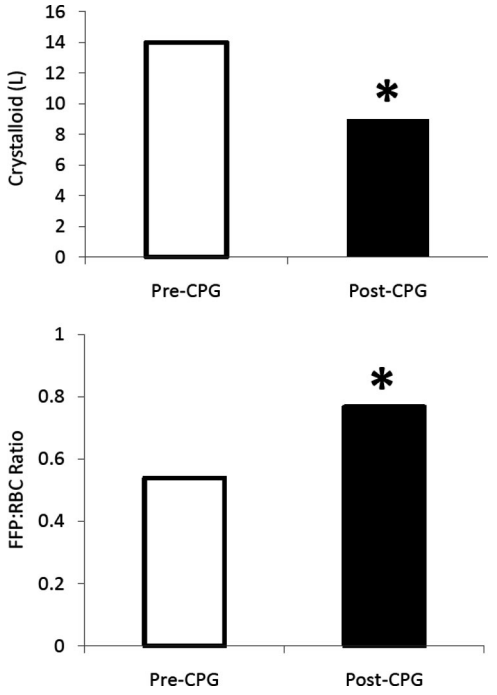

Figure 1. Crystalloid use and FFP:RBC ratio in the two cohorts. *$p < 0.05$.

between the groups and a larger portion of patients in the pre-CPG cohort received WB (Table 3).

The ratio of FFP:RBC was higher in the post-CPG cohort (Table 3 and Fig. 1). A greater portion of the pre-CPG group received a low ratio transfusion (20 vs. 4%; $p < 0.0001$) and a greater portion of the post-CPG group received

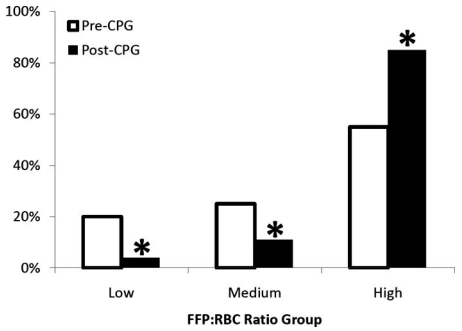

Figure 2. Percentage of casualties in each FFP:RBC ratio group. *$p < 0.05$.

a high ratio transfusion (55 vs. 85%; $p < 0.0001$; Fig. 2). The mortality rate was not significantly different between groups (24 vs. 19%; $p = 0.115$).

DISCUSSION

Implementation of the JTTS DCR CPG was associated with a change in resuscitation practice. Combat-injured MT patients are now receiving a higher ratio of FFP:RBC approximating 1.3:1, opposed to 1.9:1 early in the current conflicts. Additionally, patients are presenting warmer, with higher Hgb, and are transfused 5 L less of crystalloid. All of these differences are consistent with DCR principles that begin at the time of injury.

Blood product use depends on a variety of factors, although most of the variability lies with the physicians ordering the transfusion and the availability of product. In our study, the post-CPG group was transfused an average of 2 more units of blood, 6 more units of plasma, and 1 more unit of platelets. A side effect of the increased availability of blood components is the associated 40% decrease in transfusion of whole blood and may have had an effect on our inability to show a mortality benefit in this study as whole blood has been suggested to provide a survival benefit.[19]

Aggressive crystalloid-based resuscitation has been shown to have a variety of effects on the immunoinflammatory cascade, increased patient complications, such as intra-abdominal hypertension and abdominal compartment syndrome, and has been associated with increased risk of mortality.[20–22] The patients in the post-CPG cohort received 5 L less crystalloid, which is a decrease of >40%. This decrease is especially significant given that our mortality did not increase. DCR strategies require less intraoperative crystalloids and, by rapidly correcting coagulopathy, actually reduce overall or total blood volume transfused, although this was not seen in our study.[7,23–26]

Perhaps the greatest evidence of the impact of these guidelines was that only 4% of patients received a low ratio transfusion after the CPG was issued. We also noted an increase of >50% in the portion of patients receiving a high-ratio transfusion, which is likely skewed by some amount of survival bias. Regardless, our adherence rate to the policy consistently matches or exceeds many of the policy adherence rates found in the literature.[27–30] This rate may be due to a more hierarchical nature in military medicine com-

pared with civilian medicine and other factors to include peer-reviewed publications, multiple deployments, and vigorous advocacy. Although military providers are trusted to use their best clinical judgment, rank structure and guidance from a superior may carry more weight than a more senior provider in civilian practice. Additionally, the lack of combat trauma experience, outlined by the US Government Accounting Office report, likely influenced this improvement.[1] The ability of our deployed providers to consult clear, concise, relevant guidelines provides a level of confidence to those who are combat-inexperienced.

We also noted increased admission Hgb in the post-CPG cohort. This increase is likely multifactorial. Transport times have decreased since the beginning of the conflicts, especially in Iraq; resuscitation algorithms for the combat medic have been changed; numerous hemostatic agents have been developed; and most importantly, the C-A-T tourniquet (Composite Resources, Rock Hill, SC) was issued to each individual soldier.[31,32]

Transfusion-related complications are certainly of concern, especially in the massively transfused patient. Although this study was not designed to assess the mortality effect of transfusion ratios, other studies have shown decreased mortality with higher FFP:RBC transfusion ratios. The risks of blood transfusion can broadly be categorized as noninfectious, the most feared being transfusion-related acute lung injury (TRALI), and infectious. Infectious complications are exceedingly rare with the greatest risk being hepatitis B virus infection at 1:63,000.[33] Noninfectious complications are more common.[34,35] Although TRALI remains the most feared, its incidence is much less than febrile reactions.[36,37] Without minimizing the consequence of blood transfusion complications, all are complications of living patients. We believe that a patient who is bleeding to death should have the best resuscitation we can provide. Right now, evidence-based medicine suggests that this resuscitation is a higher plasma: RBC and limiting crystalloid. Prospective studies are needed to clarify the optimal ratio and evaluate limited crystalloid resuscitation.

During development of this study, we also noted an improvement in admission temperature of wounded casualties. The patients in the later cohort arrived almost 2°F warmer. Although preventing hypothermia is mentioned in the DCR CPG, methods for prevention and management are not specifically addressed. In October 2006, a CPG was issued with the specific goal of preventing and managing hypothermia. Given that some of the patients in our second cohort were injured before implementation of the hypothermia prevention/management CPG, our 2°F improvement is likely minimized.

Additionally, the limited number of CPGs also likely improved the adherence rate. There are currently 26 CPGs, and one CPG is specific to implementation and monitoring of CPGs (http://www.usaisr.amedd.army.mil/cpgs.html). It is important not only to consider the length and detail of each CPG during its development to ensure its ease of use by providers, but also to not overwhelm providers with too many guidelines. Care must be taken to ensure that providers feel trusted to use their own judgment and that they are given enough guidance and continuing education to ensure that their judgment is sound.

Improved adherence to guidelines has been shown when CPGs are accompanied by additional adjuncts. Conversely, those CPGs without additional training have been associated with poor adherence rates.[38–41] The JTTS has developed a comprehensive program for developing, publishing, and implementing CPGs. This extends from the subject matter experts and convened panel who debate, discuss, and write CPGs to the weekly video conferences attended by providers in theater who discuss after-action reports. Therefore, providers are frequently educated and reminded of the guidelines and the data behind their issuance. Additionally, this system also allows a forum for feedback from downrange providers up the chain. This model effectively creates closed-loop feedback, which is essential for a successful system.

This study has the inherent limitations of a retrospective study and is restricted by data that were available and collected during the study period. Other unmeasured variables that may have also contributed to the change documented here were the maturity of the battlefield, the increased availability of blood products in later iterations of the war, multiple deployments of the same physicians, or increased awareness of clinicians to the literature. Nevertheless, there is a strong association with CPG implementation and adherence to DCR principles.

CONCLUSION

For any guideline to succeed in its goal, certain prerequisites must be met. First, the guideline must be up-to-date with the current state of the literature and written by subject matter experts to a level understandable by the general provider. Later iterations of the DCR CPG incorporated recommendations on platelet transfusions after data suggested improvement with earlier, more aggressive platelet transfusion.[42,43] Second, whether it is to primary care providers diagnosing breast cancer or combat medics treating our wounded service personnel, CPGs must be pushed far forward in the treatment chain. Finally, feedback mechanisms must be in place to evaluate the CPGs effectiveness so that deficiencies in the CPG or in the system itself can be remedied. The JTTS meets all of these requirements, and our study has demonstrated that a trauma system with global reach can make a tangible impact on trauma care.

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DISCUSSION

Dr. Alan Murdock (Lackland Air Force Base, San Antonio, TX): I would commend greatly the authors for addressing and pursuing the not-so glamorous topics of clinical practice guideline (CPG) implementation and process improvement. Briefly, this retrospective study evaluated pre and post the impact of implementation of a damage control resuscitation practice guideline on US combat casualties requiring massive transfusions. The primary outcomes were

plasma:blood ratios and crystalloid volume use. The study clearly demonstrated that the post-CGP date group had statistically significantly higher plasma:blood ratios, particularly in the high ratio group, and lower crystalloid volume infused. It is certainly reasonable that the CPG contributed to practice change as evident by the 40% reduction in whole-blood use. However, the study also likely demonstrates that CPG change may or may not lead to the true desired outcome. If the desired outcome was to reduce whole-blood transfusions, then this CPG was highly successful and the Defense Health Board recommendations were fulfilled. However, if the outcome was reduced mortality or even morbidity, it is still unclear based on this study that this damage control resuscitation (DCR) CPG is truly achieving its ultimate goal since there was no difference in mortality despite increased plasma:blood ratios and less crystalloid infused. However, this should not deter from the authors' key statements in their conclusions, which I have paraphrased here: First, CPGs should be fluid and readily updated based on sound data. Second, CPGs need to be publicized, accessible, and trainable. And finally, a process improvement program that includes a feedback mechanism is vital to ensure that the CPGs are truly addressing the desired outcomes.

I would appreciate if you could address the following questions:

1. Population eligible for this study only included US casualties. Why did you exclude local national population (i.e., army, police, civilians) since mortality was not the primary endpoint?
2. Since the continuity of documentation between Level II and Level III facilities can and was an issue, particularly in the early phases of Operation Iraqi Freedom/Operation Enduring Freedom, do you believe that poorer document compliance may have contributed to the difference in crystalloid volumes or any other data points you have presented?
3. Post-CPG group received 5 L less of crystalloid. The manuscript states this is "especially significant since the mortality did not increase." Proponents for limited blood transfusions would argue that since there was not mortality difference, how could you justify placing these patients at risk for blood transfusion complications? How would you address their concerns? DCR CDP identifies five early risk factors for massive transfusion based on heart rate, systolic blood pressure, temperature, international normalization ratio, and pH. You chose to use base deficit (BD) in your data demographics. Why did you choose BD instead of pH, and did you look at initial pH? Is so, was pH not statistically different between pre- and post-CPG groups?
4. Although mortality was a not a primary outcome, as the mortality rate pre- and post-CPG showed no difference but there was a profound reduction by 40% in whole- blood use, do you believe your study supports the use of whole blood for massive transfusion to reduce mortality?
5. Finally, one last comment: I would not minimize the finding that post-CPG—in particular, the October 2006 Hypothermia CPG—has led to a significant reduction on hypothermia, almost 2° increase with an extremely small standard deviation. This finding certainly stresses the fact that a CPG can have a huge impact on clinical practice.

Dr. John W. Simmons (Brooke Army Medical Center, Fort Sam Houston, TX): Thank you for your comments. The following paragraphs respond to your questions.

The database used for this retrospective study is maintained at the US Army Institute of Surgical Research and includes only US military personnel. Including local nationals would have certainly increased our study population; however, the goal of this study was to evaluate the effect of CPG implementation and not necessarily to show a mortality difference.

As with any retrospective study, the quality of the data is of vital importance. The data included in the database used for this study has gone through quality assurance by the US Army Institute of Surgical Research. Additionally, the time bias alluded to would tend to favor a lower volume resuscitation in the pre-CPG cohort because of poor data fidelity, missing data. With regard to transfusion numbers, the time bias is likely less of an issue given that red blood cells (RBCs) and plasma are more closely regulated than bags of saline.

We did not look at initial pH. This has more to do with data validity than anything else. Some patients had venous blood gase on admission, some had areterial blood gases, and some had nothing documented until later in the hospital course. The most consistent laboratory value to assess for cellular hypoperfusion in this patient population was the base deficit.

The reduction in whole-blood use in our study was the effect of a more developed trauma system with resultant increase in the availability of packed RBCs. Although all active-duty military are screened for communicative diseases, the risks of whole-blood transfusion are higher than of packed cells. A recent article published in the *Journal of Trauma* by Spinella et al. showed a mortality benefit from fresh whole blood. They hypothesize that the improved survival is likely from reduced additives and anticoagulants compared with packed RBCs. Our study is likely biased by the increased use of fresh whole blood in the earlier cohort.

Managing a global trauma system is a difficult task, and it is vitally important to critically evaluate the influence that system managers have on the system itself. In both instances, DCR and hypothermia, the Joint Theater Trauma System was able to identify an area with room for improvement and, through evidence based medicine, create and implement a solution that had a tangible impact on the patient half a world away.